



Noncirrhotic Portal Hypertension: Medical and Endoscopic Management

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Overview

Noncirrhotic portal hypertension (NCPH) encompasses primarily diverse vascular disorders that lead to portal hypertension (PHT) with normal synthetic liver function and normal or mild elevation in hepatic venous pressure gradient.¹ Disorders leading to NCPH are classified by site of resistance to blood flow as shown in Table 1.

The most common causes of NCPH are extrahepatic portal vein obstruction (EHPVO), noncirrhotic portal fibrosis (NCPF; or idiopathic PHT [IPH]), and schistosomiasis.² IPH or NCPF is a primary cause of NCPH, unlike many diseases such as primary biliary cirrhosis or hepatic venous outflow obstruction, where PHT is secondary. NCPF (as is known in the Indian subcontinent), IPH (in Japan and South Eastern countries), and hepatoportal sclerosis (in Western countries) broadly resemble each other.³ The general characteristics of patients with NCPH are shown in Table 2.

Etiopathogenesis and Histological Characteristics

Etiopathogenesis of NCPF/IPH varies among regions: infections (*Escherichia coli*, poor living conditions) as causal associations in the eastern areas with additional immunological factors implicated in Japanese populations, prothrombotic states and toxic exposures (vitamin A, arsenic, thiopurine derivatives) predominating in western regions (low prevalence, better social and economic conditions), and genetic (Adams-Oliver syndrome, Turner syndrome, phosphomannose isomerase deficiency) associations and familial clustering (HLA-DR3) seen among Indian and western populations. The *unifying hypothesis* proposes infection/inflammation as a precipitating event in a prothrombotic individual in both EHPVO and NCPF: a major thrombotic event occurring at a young age involving the main portal vein and causing EHPVO and repeated microthrombotic

TABLE 1 Causes of NCPH

Prehepatic

HVPG normal, PVP high, ISP high
EHPVO Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Infiltrative diseases
Storage disorders

Hepatic

WHVP normal/high, HVPG normal or high, PVP high, ISP high

Presinusoidal

Adult polycystic disease
Hereditary hemorrhagic telangiectasia
Arteriovenous fistulas
Congenital hepatic fibrosis
Autoimmune cholangiopathy
Sclerosing cholangitis
Toxic vinyl chloride
Malignant obstruction of portal venous system
Granulomatous diseases of liver
Hepatoportal sclerosis (NCPF, IPH)
Peliosis hepatitis
Partial nodular transformation

Sinusoidal

Alcoholic hepatitis
Drug-induced liver injury
Toxin-mediated liver injury
Metabolic liver disease
Infectious hepatitis
Infiltrative liver disease
Diseases causing sinusoidal compression (Gaucher's disease, leishmaniasis)

Postsinusoidal

Veno-occlusive disease
Primary vascular malignancies
Granulomatous phlebitis
Budd-Chiari syndrome

Posthepatic

FHVP high, RAP normal or high, WHVP high, HVPG normal or high, PVP high, ISP high

Inferior vena cava obstruction
Constrictive pericarditis
Tricuspid regurgitation
Severe right-sided heart failure
Restrictive cardiomyopathy

Abbreviations: FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; ISP, intrasplenic pressure; PVP, portal venous pressure; RAP, right atrial pressure; WHVP, wedged hepatic venous pressure.

events during adolescence involving medium and small branches of portal vein leading to NCPF. The *dual theory*, as proposed in the western population, states that increased splenic blood flow and intrahepatic obstruction may play a role in IPH. As per *endothelial-mesenchymal transition theory*

Abbreviations: BB, beta-receptor blocker; EHPVO, extrahepatic portal vein obstruction; EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; IPH, idiopathic portal hypertension; NCPF, noncirrhotic portal fibrosis; NCPH, noncirrhotic portal hypertension; PHT, portal hypertension.

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TABLE 2 Differences and Characteristics of NCPF Versus EHPVO

Characteristics	NCPF/IPH	EHPVO
Nature of precipitating event in lieu with genetic predisposition, infections, or prothrombotic state	Mild, recurring	Severe, acute, progressive
Affected population	Childhood, adolescence	Neonatal, early childhood
Affected regions	Western countries and also Japan	Eastern regions, most commonly India
Median age	28--32 years	10--16 years
Autoimmune features	Yes	No
Splenomegaly	Disproportionate and massive	Mild to moderate
Encephalopathy	Usually absent, except in end-stage liver disease	Minimal encephalopathy occurs as part of natural history of disease
Growth retardation	Usually not seen	Commonly seen in prepubertal disease
Portal biliopathy	Uncommon	90%-100%
Hepatic venous pressure gradient	Slightly elevated sometimes	Normal
USG features	Patent splenoportal axis, thickened and dilated portal vein, periportal fibrosis, massive splenomegaly	Portal vein thrombosis with varying degrees of thrombosis involving splenic and mesenteric veins; portal cavernoma formation in mandatory
Histology	Portal sclerosis or hepatoportal sclerosis, obliterative portovenopathy	Unremarkable, or mild periportal fibrosis
	Essential for diagnosis	Helpful in adult EHPVO

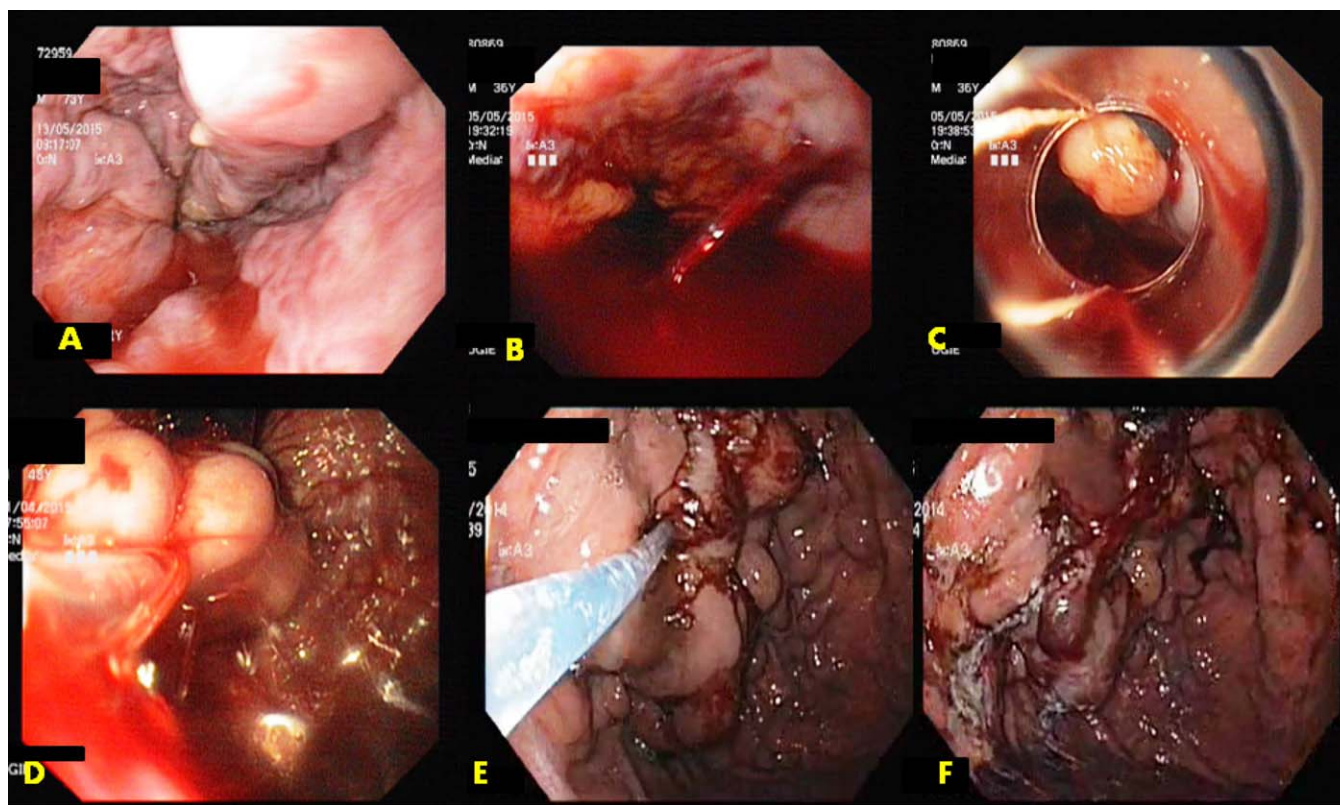


Figure 1 A, Large, oozing varices in a patient with EHPVO. B, Active spurt from large varices in patient with EHPVO. C, Endoscopic band ligation over the spurting varix resulting in hemostasis. D, Spurting gastroesophageal varix (GOV) 2 with blood gushing into the injector during cyanoacrylate glue therapy. E, Glue therapy for large, oozing GOV 1 followed by (F) hemostasis after glue cast formation.

(Japan), the vascular endothelial cells of portal venules transition to myofibroblastic cells, leading to excessive synthesis of collagen type 1 promoting obliterative venopathy and presinusoidal PHT.⁴

In EHPVO, the cause also varies between paediatric and adult populations with prothrombotic state (commonly methylenetetrahydrofolate reductase (MHTFR), protein C, S, and antithrombin III mutations), with intra-abdominal

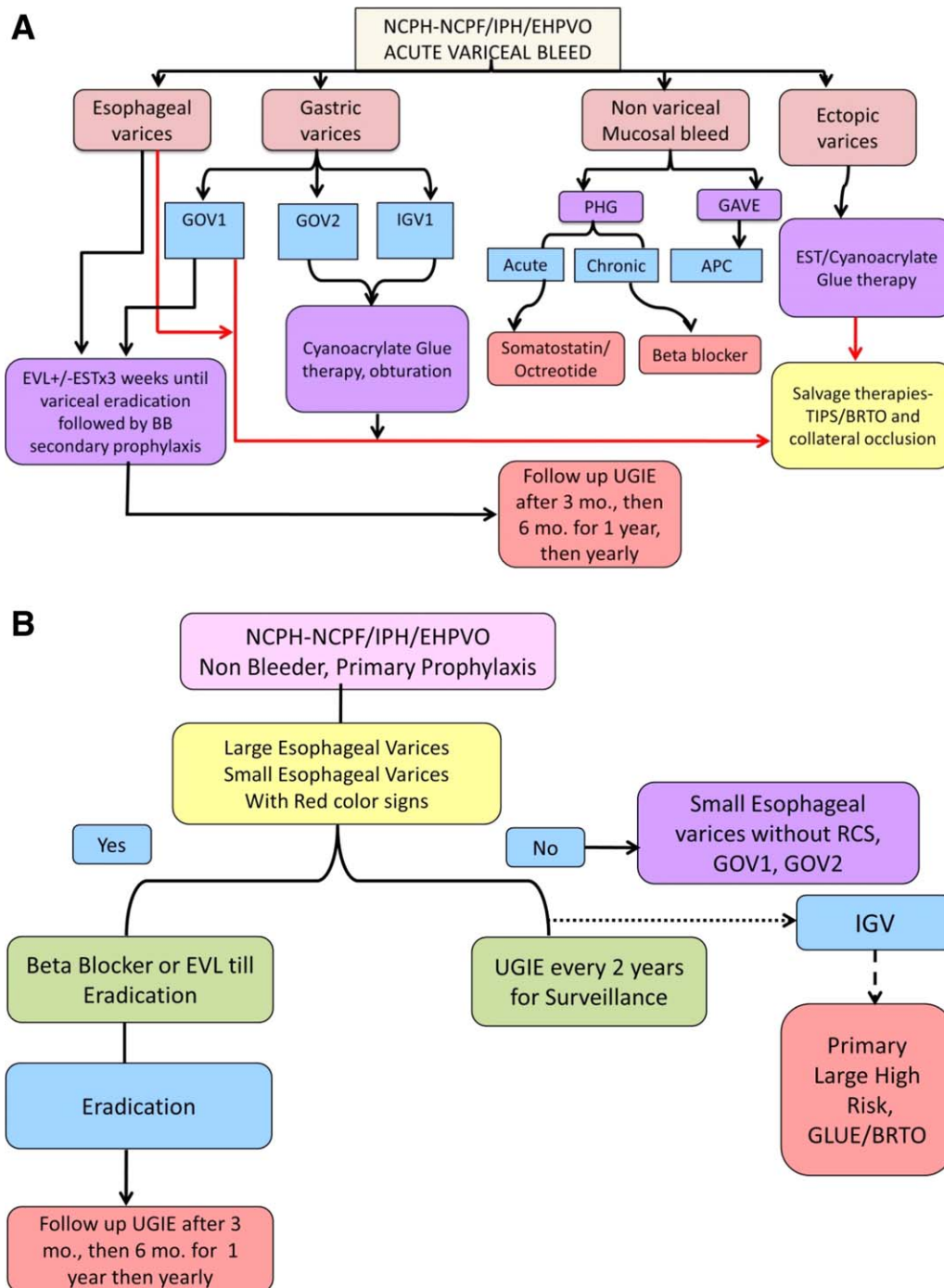


Figure 2 A, Algorithmic management of a bleeding patient with NCPH. Red lines indicate in case of failure of medical or endotherapy. B, Algorithmic management in primary prophylaxis in a patient with NCPH with variceal disease. Abbreviations: APC, argon plasma coagulation; BRTO, balloon, occluded transvenous obliteration; EVL, endoscopic band ligation; GAVE, gastric antral vascular ectasia; GOV, gastroesophageal varices; IGV, isolated gastric varix; PHG, portal hypertensive gastropathy; TIPS, transjugular, intrahepatic portosystemic shunt; UGIE, upper gastrointestinal endoscopy. A, Adapted from *Journal of Hepatology*.⁶ Copyright 2014, European Association for the Study of the Liver.

infections predominating in the former and myeloproliferative disorders with or without JAK2 mutations in the latter, even though from 68% to 72% of both children and adults do not showcase causality even after extensive evaluation.⁵

Even though needle biopsy of the liver may be unremarkable, the autopsy or explant biopsy in NCPF/IPH reveals phlebosclerosis (100% of cases), fibroelastosis, perisinusoidal and periportal fibrosis, portal angiomatosis, dilated

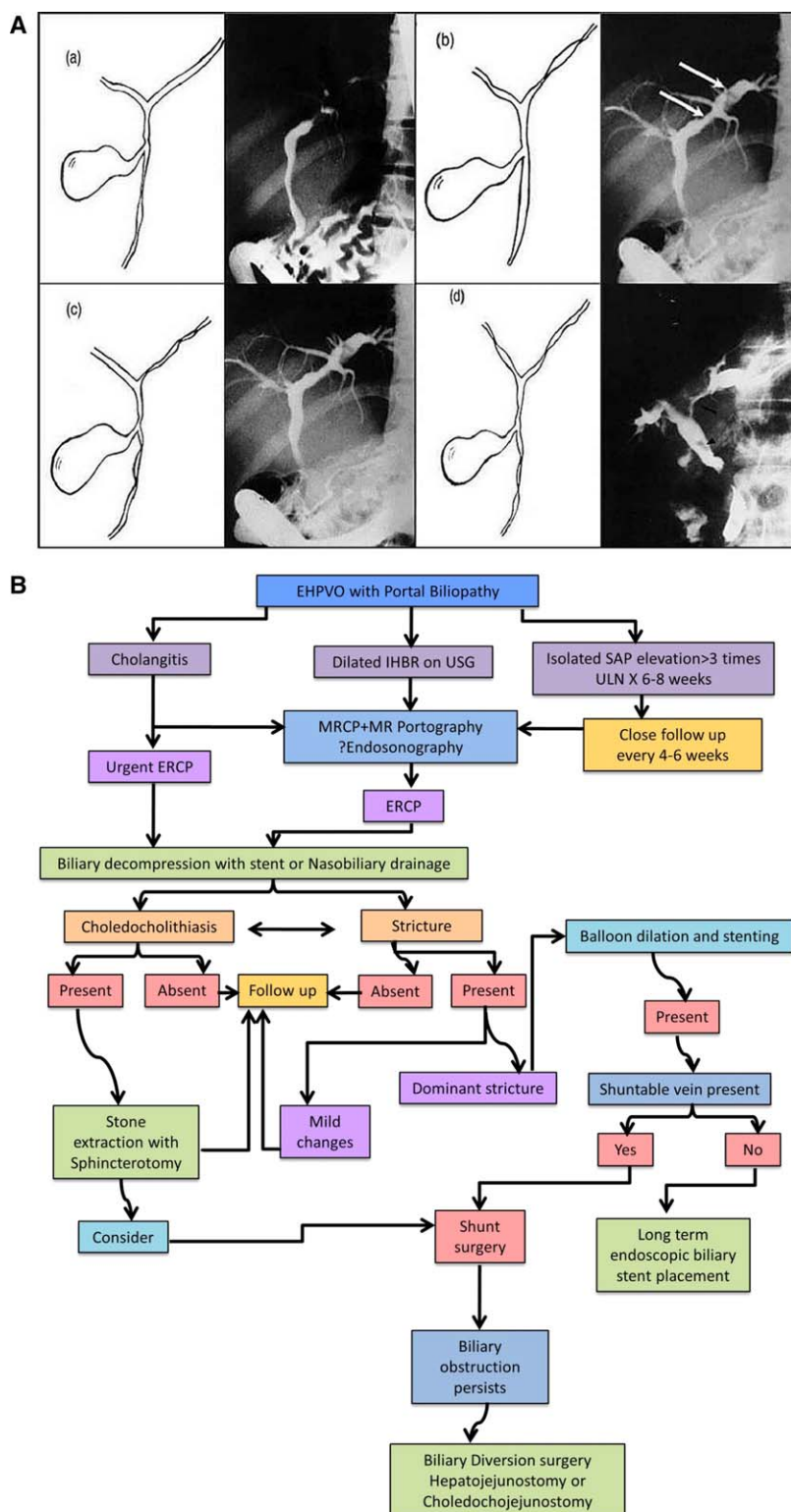


Figure 3 A, Classification of portal biliopathy and schematic representation in a patient with NCPH/EHPVO. Classification of portal biliopathy in EHPVO: (a) type I, involvement of extrahepatic bile duct; (b) type II, involvement of intrahepatic bile ducts only; (c) type IIIa, involvement of extrahepatic bile duct and unilateral intrahepatic bile duct (left or right); and (d) type IIIb, involvement of extrahepatic bile duct and bilateral intrahepatic ducts. B, Algorithmic management of portal biliopathy in a patient with NCPH/EHPVO. ERCP, endoscopic retrograde cholangiopancreatography; GOV, gastroesophageal varices; IHBR, intrahepatic biliary radicles; MRCP, magnetic resonance cholangiopancreatography; SAP, serum alkaline phosphatase. A, Reproduced from Chandra R, Kapoor D, Tharakan A, Chaudhary A, Sarin SK. Portal biliopathy. *J Gastroenterol Hepatol* 2001;16:1086-1092; *Journal of Gastroenterology and Hepatology*. Copyright 2001, Asian Pacific Association of Gastroenterology. B, Adapted from *Journal of Hepatology*.⁶ Copyright 2014, European Association for the Study of the Liver.



thickened sclerotic portal vein with thrombosis in medium and small portal venules, and radicles (histological hallmark is obliterative portovenopathy). In EHPVO, grossly, there is cavernomatous transformation of the main portal vein with biopsy revealing mild periportal fibrosis.⁶ In the West, EHPVO is an adulthood disease and is an uncommon cause of variceal bleeding, whereas in the East, it is a disease of children, often presenting with variceal bleed and growth retardation. In late stages, low serum albumin, deranged international normalized ratio, and disseminated intravascular coagulopathy develop. Patients with IPH/NCPF commonly present with recurrent, well-tolerated variceal bleeding, anemia, lump in left upper quadrant, and hypersplenism with preserved liver functions.⁷

Medical and Endoscopic Management

The key approach to management in NCPF and EHPVO is to control acute variceal bleeding and prevent rebleeding (Figure 1). In EHPVO, in addition, splenomegaly and hypersplenism, growth failure, minimal hepatic encephalopathy, and portal biliopathy need attention. The medical management of acute variceal bleeding in NCPH follows hemodynamic stability, airway protection, and use of vasoactive drugs such as terlipressin, somatostatin, or octreotide followed by endotherapy. Endoscopic sclerotherapy (EST) and endoscopic variceal ligation (EVL) have been shown to have equal efficacy (80%-90%) in controlling acute bleeding.⁸ A randomized control trial in NCPH showed equal efficacy of propranolol and EVL for preventing rebleed episodes. Gastric varices are more common in patients who bleed because of EHPVO (about 40%) and NCPF than because of cirrhosis. Cyanoacrylate glue injection most often controls the acute gastric varix bleeds. However, nearly 10% of cases need rescue therapies such as transjugular intrahepatic portosystemic shunts, bal-

loon occluded retrograde transvenous obliteration of varices, devascularization, or a decompression shunt (Fig. 2A,B).

Whereas in patients with acute portal thrombosis, use of anticoagulants is well established, in longstanding thrombosis of portal vein, EHPVO, or in NCPF, with underlying procoagulant state, no consensus exists on the routine long-term use of anticoagulants. Their use should, however, be considered in patients who are at high risk for thrombosis progression and in whom adequate management of varices has been achieved. In patients with EHPVO with symptomatic portal biliopathy, relieving biliary obstruction and cholangitis with nasobiliary drainage/stenting/stone extraction and repeated dilation of strictures is often required (Fig. 3A,B). Unlike NCPF/IPH, EHPVO of childhood is a progressive disease with slow parenchymal extinction and development of ascites. Proximal lienorenal shunt surgery and Rex-bypass should be considered, if expertise and shuntable veins are available. The former decompresses and treats the hypersplenism, whereas the latter improves growth failure and prevents rebleed. The 10-year survival rate in treated EHPVO is around 80%, whereas in NCPF/IPH it ranges from 85% to 95%.^{9,10}

Conclusions

NCPH is a term describing a heterogeneous vascular disorder of the liver that includes generally patients with NCPF (in the East), IPH (in the West), and EHPVO. Although the etiopathogenesis may differ, the clinical syndromes are distinct and easily diagnosed. Workup and treatment of procoagulant state is useful. Endoscopic management of acute variceal bleed and prevention of rebleed improve survival. Interventional radiological techniques and surgical treatment offer useful rescue therapies.■

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